

ONLINE SEARCH REQUEST FORM

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USER Wesley Feix SERIAL NUMBER 715272  
ART UNIT 1806 PHONE 2731 DATE 9/11/92

Please give a detailed statement of requirements. Describe as specifically as possible the subject matter to be searched. Define any terms that may have special meaning. Give examples or relevant citations, authors, or keywords, if known.

You may include a copy of the broadest and or relevant claim(s).

Please search  
Making Humanized Antibodies  
by - CDR: Grafting - ~~and~~

~~by - CDR: Grafting - and~~

See claims 1-13  
Especially !!!

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9/15/92

Feisel  
715272

File 155: MEDLINE 1966-1992/NOV (9211W1)  
File 5: BIOSIS PREVIEWS 69-92/OCT BA9407: BARRM4307  
(C. BIOSIS 1992)  
File 73: EMBASE (EXCERPTA MEDICA) 74-92/ISS37  
(COPR. ESP BV/EM 1992)  
File 399: CA SEARCH 1967-1992 UD=11710  
(Copr. 1992 by the Amer. Chem. Soc.)

?ds

Set	Items	Description
S1	16	HUMANIZED() ANTIBODIES/TI
S2	332298	ANTIBODIES! FROM 155
S3	2253	IMMUNOGLOBULIN VARIABLE REGION! FROM 155
S4	2253	S2 AND S3
S5	862	HUMANIZ?
S6	2005	HUMANIS?
S7	16	S4 AND (HUMANIZ? OR HUMANIS?)
S8	636823	ANTIBOD? FROM 5,73,399
S9	165469	IMMUNOGLOBULIN
S10	41830	IG
S11	113462	VARIABLE
S12	392448	REGION
S13	862	(IMMUNOGLOBULIN OR IG) (W) VARIABLE (W) REGION
S14	604	CDR
S15	67991	COMPLEMENTARY
S16	112646	DETERMINING
S17	63	COMPLEMENTARY (W) DETERMINING
S18	1904	HYPERVARIABLE
S19	392448	REGION
S20	747	(COMPLEMENTARY (W) DETERMINING OR HYPERVARIABLE) (W) REGION
S21	428778	ANTIBODY
S22	1469126	RELATED
S23	623755	BINDING
S24	544344	SITE? ?
S25	0	ANTIBODY (W) RELATED (W) BINDING (W) SITE? ?
S26	2161	(IMMUNOGLOBULIN OR IG) () VARIABLE () REGION OR CDR OR (COMPLEMENTARY () DETERMINING OR HYPERVARIABLE) () REGION OR ANTIBODY () RELATED () BINDING () SITE? ? FROM 5,73,399
S27	897	8 AND 26
S28	18	27 AND (5 OR 6)
S29	34	28 OR 7
S30	21	RD (unique items)
S31	21	Sort S30/ALL/PY,D

?t31/7/1-21

*synonym for CDR*

*synonyms for CDR*

31/7/1 (Item 1 from file: 5)  
9568885 BIOSIS Number: 94073885  
\*HUMANIZED\* OKT3 \*ANTIBODIES\* SUCCESSFUL TRANSFER OF IMMUNE MODULATING  
PROPERTIES AND IDIOTYPE EXPRESSION  
WOODLE E S; THISTLEWAITE J R; JOLIFFE L K; ZIVIN R A; COLLINS A; ADAIR J  
A; BODMER M; ATHWAL D; ALEGRE M-L; BLUESTONE J A  
SECT. ORGAN TRANSPLANTATION, DEP. SURGERY, WASH. UNIV. SCH. MED., ONE  
BARNES HOSP. PLAZA, QUEENY TOWER, SUITE 6107, ST. LOUIS, MO. 63110.  
J IMMUNOL 148 (9). 1992. 2756-2763. CODEN: JOIMA  
Full Journal Title: Journal of Immunology  
Language: ENGLISH

..\*Antibodies\* that possess the Ag-binding regions of OKT3 within the context of a human framework (Hu-OKT3 Ab) offer distinct advantages for optimizing anti-CD3 mAb therapy. First, manipulation of Ab genes to produce \*humanized\*. Ab that retain Ag-binding activity may circumvent antigenicity problems. Second, Ab gene engineering provides a means for modifying functional properties, including T cell activation and immune suppression. The purpose of this study was to determine the functional properties of Hu-OKT3 Ab and to compare the functional properties and idiotypes of Hu-OKT3 Ab to those of murine OKT3. Three Hu-OKT3 IgG4 aAb, a chimeric OKT3 \*antibody\* (cOKT3-1) (grafted sequences comprising all OKT3 VH and VL regions) and two complementarity determining region (\*CDR\*)-grafted \*antibodies\* , gOKT3-5 and gOKT3-6 (grafted sequences comprising only OKT3 VH and VL \*CDR\* and some framework amino acids, were analyzed. Initial studies demonstrated that the cOKT3 and gOKT3-5 Ab bound selectively to T cells and competitively inhibited OKT3-FITC binding with avidities similar to that of murine OKT3. binding avidity of the gOKT3-6 Ab was markedly less than that of the other Hu-OKT3 Ab. Serologic analysis suggested that cOKT3 and gOKT3-5 Ab possess idiotypes (combining sites) similar to murine OKT3. C cell activation potency of all three Hu-OKT3 Ab was assessed by proliferation, induction of activation marker expression (IL-2R and Leu 23), and lymphokine production (TNF-.alpha. and IFN-.gamma.). The cOKT3 and gOKT3-5 Ab demonstrated T cell activation potencies similar to murine OKT3 as assessed by each parameter. CD3 coating and modulation by these two Ab was effective but somewhat less potent than that observed with OKT3. Finally, cOKT3 and gOKT3-5 Ab both inhibited CTL activity comparably to murine OKT3. In conclusion, these studies indicate that gOKT3-5 and cOKT3 Ab possess immune modulating properties similar to murine OKT3 and thus offer attractive alternatives to murine OKT3 for in vivo therapy.

31/7/2 (Item 2 from file: 155)  
08124424 92262424

\*Humanization\* of an anti-p185HER2 antibody for human cancer therapy.  
Carter P; Presta L; Gorman CM; Ridgway JB; Henner D; Wong WL; Rowland AM;  
Kotts C; Carver ME; Shepard HM  
Department of Protein Engineering, Genentech Inc., South San Francisco,  
CA 94080.

Proc Natl Acad Sci U S A (UNITED STATES) May 15 1992, 89 (10) p4285-9,  
ISSN 0027-8424 Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The murine monoclonal antibody mumAb4D5, directed against human epidermal growth factor receptor 2 (p185HER2), specifically inhibits proliferation of human tumor cells overexpressing p185HER2. However, the efficacy of mumAb4D5 in human cancer therapy is likely to be limited by a human anti-mouse antibody response and lack of effector functions. A "\*humanized\*" antibody, humAb4D5-1, containing only the antigen binding loops from mumAb4D5 and human variable region framework residues plus IgG1 constant domains was constructed. Light- and heavy-chain variable regions were simultaneously \*humanized\* in one step by "gene conversion mutagenesis" using 311-mer and 361-mer preassembled oligonucleotides, respectively. The humAb4D5-1 variant does not block the proliferation of human breast carcinoma SK-BR-3 cells, which overexpress p185HER2, despite tight antigen binding ( $K_d = 25$  nM). One of seven additional \*humanized\* variants designed by molecular modeling (humAb4D5-8) binds the p185HER2 antigen 250-fold and 3-fold more tightly than humAb4D5-1 and mumAb4D5, respectively. In addition, humAb4D5-8 has potency comparable to the murine antibody in blocking SK-BR-3 cell proliferation. Furthermore, humAb4D5-8 is much more efficient in supporting antibody-dependent cellular cytotoxicity against SK-BR-3 cells than mumAb4D5, but it does not efficiently kill WI-38 cells, which express p185HER2 at lower levels.

31/7/3 (Item 3 from file: 155)

08081267 92219267

Antibody framework residues affecting the conformation of the hypervariable loops.

Footnote J; Winter G

MRC Laboratory of Molecular Biology, Cambridge, England.

J Mol Biol (ENGLAND) Mar 20 1992, 224 (2) p487-99, ISSN 0022-2836

Journal Code: J6V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Rodent monoclonal antibodies have been "*\*humanized\**" or "reshaped" for therapy by transplanting the antigen-binding loops from their variable domains onto the beta-sheet framework regions of human antibodies. However, additional substitutions in the human framework regions are sometimes required for high affinity antigen binding. Here we describe antigen binding by a reshaped antibody derived from the mouse anti-lysozyme antibody D1.3, and several variants in which point mutations had been introduced into framework positions to improve its affinity. The affinities were determined from the relaxation kinetics of reactant mixtures using quenching of fluorescence that occurs upon formation of the antibody-antigen complex. The dissociation constant of lysozyme ranged from 3.7 nM (for D1.3) to 260 nM. Measurement of antibody-antigen association kinetics using stopped-flow showed that D1.3 and most of the reshaped antibodies had bimolecular rate constants of  $1.4 \times 10^6 \text{ s}^{-1} \text{ M}^{-1}$ , indicating that differences in equilibrium constant were predominantly due to different rates of dissociation of lysozyme from immune complexes. Mutations in a triad of heavy chain residues, 27, 29 and 71, contributed 0.9 kcal/mol in antigen binding free energy, and a Phe to Tyr substitution of light chain residue 71 contributed an additional 0.8 kcal/mol. The combined effect of all these mutations brought the affinity of the reshaped antibody to within a factor of 4 of D1.3. All of these substitutions were in the beta-sheet framework closely underlying the complementarity-determining regions, and do not participate in a direct interaction with antigen. The informed selection of residues in such positions may prove essential for the success of loop transplants in antibodies. Variation of these sites may also have a role in shaping the diversity of structures found in the primary repertoire, and in affinity maturation.

31/7/4 (Item 4 from file: 155)

08010135 92148135

Chimeric and *\*humanized\** antibodies with specificity for the CD33 antigen.

Co MS; Avdalovic NM; Caron PC; Avdalovic MV; Scheinberg DA; Queen C  
Protein Design Labs, Inc., Mountain View, CA 94043.

J Immunol (UNITED STATES) Feb 15 1992, 148 (4) p1149-54, ISSN 0022-1767 Journal Code: IFB

Contract/Grant No.: NIH CA55349

Languages: ENGLISH

Document type: JOURNAL ARTICLE

L and H chain cDNAs of M195, a murine mAb that binds to the CD33 Ag on normal and leukemic myeloid cells, were cloned. The cDNAs were used in the construction of mouse/human IgG1 and IgG3 chimeric antibodies. In addition, *\*humanized\** antibodies were constructed which combined the complementarity-determining regions of the M195 antibody with human framework and constant regions. The human framework was chosen to maximize homology with the M195 V domain sequence. Moreover, a computer model of M195 was used to identify several framework amino acids that are likely to interact with the complementarity-determining regions, and these residues

were also retained in the \*humanized\* antibodies. Unexpectedly, the \*humanized\* IgG1 and IgG3 M195 antibodies, which have reshaped V regions, have higher apparent binding affinity for the CD33 Ag than the chimeric or mouse antibodies.

31/7/5 (Item 5 from file: 155)

07996790 92134790

Gene conversion of immunoglobulin variable regions in mutagenesis cassettes by replacement PCR mutagenesis.

Near RI

Cellular and Molecular Research Laboratory, Massachusetts General Hospital, Boston 02144.

Biotechniques (UNITED STATES) Jan 1992, 12 (1) p88-97, ISSN 0736-6205  
Journal Code: AN3

Contract/Grant No.: HL-19259

Languages: ENGLISH

Document type: JOURNAL ARTICLE

A technique, Replacement PCR Mutagenesis, was developed to replace one immunoglobulin variable region (V) in a M13 phage cassette with a different, homologous V. This allows the use of the same mutagenesis and subsequent expression vectors for many V regions or V segments. The method combines PCR of V fragments and in vitro mutagenesis. Primers homologous to 3' and 5' ends of both V regions initiate PCR synthesis of the V DNA fragment (donor) that will replace the V region (recipient) in M13. Donor V PCR DNA may originate from mRNA, cloned V genes or genomic templates. The donor V PCR DNA is denatured and annealed to the M13 cassette containing the recipient V to be supplanted. The second strand is synthesized, transfected into bacteria and mutant plaques selected by hybridization. Since restriction sites in primers are not required, altered primer-encoded amino acids are avoided. Further, the PCR donor piece can be of any length if it shares homology with the recipient gene. This allows construction and expression of complete gene replacements and chimeras. This method is also applicable to V "\*humanization\*" and studying sets of homologous genes containing polymorphic or evolutionary disparities. The potential uses of the technique are discussed.

31/7/6 (Item 6 from file: 5)

8779979 BIOSIS Number: 42004979

IMMUNOHISTOCHEMICAL CHARACTERIZATION OF THE \*CDR\*-GRAFTED \*HUMANIZED\* MONOCLONAL \*ANTIBODY\* BW 431-26 HUMAB PRECLINICAL STUDY

MASCHEK W; BOSSLET K

INST. NUCLEARMED., LINZ BEHRING RES. LABS, MARBURG, FRG.

EUROPEAN ASSOCIATION OF NUCLEAR MEDICINE CONGRESS, VIENNA, AUSTRIA, SEPTEMBER 1-5, 1991. EUR J NUCL MED 18 (8). 1991. 546. CODEN: EJNMD

Language: ENGLISH

31/7/7 (Item 7 from file: 5)

8563624 BIOSIS Number: 92028624

POLYMERASE CHAIN REACTION FACILITATES THE CLONING \*CDR\*-GRAFTING AND RAPID EXPRESSION OF A MURINE MONOCLONAL \*ANTIBODY\* DIRECTED AGAINST THE CD18 COMPONENT OF LEUKOCYTE INTEGRINS

DAUGHERTY B L; DEMARTINO J A; LAW M-F; KAWKA D W; SINGER I I; MARK G E  
DEP. CELL. MOL. BIOL., MERCK SHARP DOHME RES. LAB., RAHWAY, N.J. 07065, USA.

NUCLEIC ACIDS RES 19 (9). 1991. 2471-2476. CODEN: NARHA

Full Journal Title: Nucleic Acids Research

Language: ENGLISH

Two novel approaches of recombinant PCR technology were employed to graft the complementarity determining regions from a murine monoclonal \*antibody\* (mAb) onto human \*antibody\* frameworks. One approach relied on the

availability of cloned human variable region templates, whereas the other strategy was dependent only on human variable region protein sequence data. The transient expression of recombinant \*humanized\* \*antibody\* was driven by the adenovirus major late promoter and was detected 48 hrs post-transfection into non-lymphoid mammalian cells. The application of these new approaches enables the expression of a recombinant \*humanized\* \*antibody\* just 6 weeks after initiating the cDNA cloning of the murine mAB.

31/7/8 (Item 8 from file: 155)  
08049594 92187594

\*Humanization\* of a mouse monoclonal antibody by CDR-grafting: the importance of framework residues on loop conformation.

Kettleborough CA; Saldanha J; Heath VJ; Morrison CJ; Bendig MM

Medical Research Council Collaborative Centre, London, UK.

Protein Eng (ENGLAND) Oct 1991, 4 (7) p773-83, ISSN 0269-2139

Journal Code: PR1

Languages: ENGLISH

Document type: JOURNAL ARTICLE

A mouse monoclonal antibody (mAb 425) with therapeutic potential was ' \*humanized\* ' in two ways. Firstly the mouse variable regions from mAb 425 were spliced onto human constant regions to create a chimeric 425 antibody. Secondly, the mouse complementarity-determining regions (CDRs) from mAb 425 were grafted into human variable regions, which were then joined to human constant regions, to create a reshaped human 425 antibody. Using a molecular model of the mouse mAb 425 variable regions, framework residues (FRs) that might be critical for antigen-binding were identified. To test the importance of these residues, nine versions of the reshaped human 425 heavy chain variable (VH) regions and two versions of the reshaped human 425 light chain variable (VL) regions were designed and constructed. The recombinant DNAs coding for the chimeric and reshaped human light and heavy chains were co-expressed transiently in COS cells. In antigen-binding assays and competition-binding assays, the reshaped human antibodies were compared with mouse 425 antibody and to chimeric 425 antibody. The different versions of 425-reshaped human antibody showed a wide range of avidities for antigen, indicating that substitutions at certain positions in the human FRs significantly influenced binding to antigen. Why certain individual FR residues influence antigen-binding is discussed. One version of reshaped human 425 antibody bound to antigen with an avidity approaching that of the mouse 425 antibody.

31/7/9 (Item 9 from file: 155)  
07969093 92107093

\*Humanization\* of monoclonal antibodies.

Gussow D; Seemann G

Methods Enzymol (UNITED STATES) 1991, 203 p99-121, ISSN 0076-6879

Journal Code: MVA

Languages: ENGLISH

Document type: JOURNAL ARTICLE

31/7/10 (Item 10 from file: 155)  
07953750 92091750

Construction, expression and characterization of \*humanized\* antibodies directed against the human alpha/beta T cell receptor.

Shearman CW; Pollock D; White G; Hehir K; Moore GP; Kanzy EJ; Kurrle R  
Genzyme Corporation, Framingham, MA 01701.

J Immunol (UNITED STATES) Dec 15 1991, 147 (12) p4366-73, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Completely \*humanized\* antibodies with specificity for the human alpha/beta TCR have been produced by genetic engineering. The L and H chain V region exons encoding the murine mAb BMA 031 CD regions and human EU framework regions were synthesized and replaced into previously isolated genomic fragments. These fragments were inserted into mammalian expression vectors containing the human kappa and gamma 1 C region exons. Two variants were constructed each containing selected BMA 031 amino acids within the human frameworks. The \*humanized\* genes were transfected into Sp2/0 hybridoma cells by electroporation and transfectomas secreting \*humanized\* antibody were isolated. Levels of antibody expression up to 7 pg/cell/24 h were obtained. The \*humanized\* antibody, BMA 031-EUCIV2, competed poorly with murine BMA 031 for binding to T cells. BMA 031-EUCIV3, however, bound specifically to T cells and competed effectively with both the murine BMA 031 antibody and a previously constructed chimeric BMA 031 antibody for binding to these cells. The relative affinity of BMA 031-EUCIV3 was about 2.5 times lower than BMA 031. The ability to promote antibody dependent cell-mediated cytotoxicity was significantly enhanced with the engineered antibodies as compared to murine BMA 031. \*Humanized\* BMA 031 is a clinically relevant, genetically engineered antibody with potential uses in transplantation, graft vs host disease, and autoimmunity.

31/7/11 (Item 11 from file: 155)  
07909485 92047485

Antigenicity of mouse monoclonal antibodies. A study on the variable region of the heavy chain.

Olsson PG; Hammarstrom L; Smith CI

Department of Clinical Immunology, Karolinska Institute, Huddinge University Hospital, Sweden.

J Theor Biol (ENGLAND) Jul 7 1991, 151 (1) p111-22, ISSN 0022-5193  
Journal Code: K8N

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Mouse monoclonal antibodies (Mabs) against human tumour antigens are currently used in therapy, but up to 50% of the patients receiving treatment form anti-Mab antibodies thus reducing the efficiency of the treatment. One attempt to minimize the immunogenicity of the mouse Mabs is to "\*humanize\*" them by replacing the constant part of the molecule with the human equivalent by genetic engineering. However, this does not reduce the immunogenicity of the variable part of the antibody. Some variable regions may be expected to be less antigenic than others. We therefore compared consensus sequences for the 11 mouse VH families with the human VH sequences published so far. Theoretical antigenicity predictions (hydrophilicity, flexibility, surface accessibility and relative antigenicity) were made and two families; VH I (J558) and VH XI (CP5 B5-3) were predicted to be immunogenic by all four methods. One family, VH X (MRL-DNA4), was not predicted to be immunogenic by any of the four methods. The residues predicted to form antigenic epitopes in the two families VH II (Q52) and VH III (36-60) are predicted not to be exposed on the surface of the antibody molecule and may therefore not be immunogenic.

31/7/12 (Item 12 from file: 5)  
7905670 BIOSIS Number: 40106670

CHIMERIC MOUSE-HUMAN AND \*CDR\*-GRAFTED \*ANTIBODIES\* TO HUMAN IL2 RECEPTOR  
WEIDLE U H; RUSSMANN E; LENZ H; KALUZA B

BOEHRINGER MANNHEIM GMBH, NONNENWALD 2, D-8122 PENZBERG, FRG.

MEETING ON MOLECULAR BIOLOGY AND THE IMMUNOPATHOGENESIS OF RHEUMATOID ARTHRITIS HELD AT THE 20TH ANNUAL MEETING OF THE KEYSTONE SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, LAKE TAHOE, CALIFORNIA, USA, MARCH 15-21, 1991. J CELL BIOCHEM SUPPL 15 (PART E). 1991. 186. CODEN: JCBSD

Language: ENGLISH

Q H 506. J67

31/7/13 (Item 13 from file: 155)  
07899816 92037816

A \*humanized\* monovalent CD3 antibody which can activate homologous complement.

Routledge EG; Lloyd I; Gorman SD; Clark M; Waldmann H  
Department of Pathology, Cambridge University.

Eur J Immunol (GERMANY) Nov 1991, 21 (11) p2717-25, ISSN 0014-2980

Journal Code: EN5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The rat monoclonal antibody (mAb) YTH12.5, specific for the CD3 antigen complex on human T cells has been modified in order to improve its efficacy in human therapy. With the aim of rendering it less immunogenic, it has been \*humanized\* using the method of framework grafting. During this process sequence analysis of the YTH12.5 VL gene indicated that it was of the lambda subclass, however, it was markedly dissimilar from previously published rat and mouse V lambda gene sequences and may represent a new V lambda gene family. The \*humanization\* of this light chain represents the first successful reshaping of a lambda light chain V region. To improve the effector function of the antibody we have created a monovalent form (1 Fab, 1 Fc) using a novel method involving the introduction of an N-terminally truncated human IgG1 heavy chain gene into cells producing the \*humanized\* CD3 mAb. Comparison of the mono- and bivalent \*humanized\* mAb in a complement-mediated cell lysis assay revealed that the monovalent antibody mediated lysis of human T cell blasts whereas the bivalent form did not. The availability of a \*humanized\*, complement-fixing CD3 mAb may improve opportunities for human therapy, in the management of organ rejection, autoimmunity and the treatment of T cell lymphoma.

31/7/14 (Item 14 from file: 155)  
07768736 91287736

A possible procedure for reducing the immunogenicity of antibody variable domains while preserving their ligand-binding properties.

Padlan EA

Laboratory of Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892.

Mol Immunol Apr-May 1991, 28 (4-5) p489-98, ISSN 0161-5890

Journal Code: NG1

Languages: ENGLISH

Document type: JOURNAL ARTICLE

It is proposed to reduce the immunogenicity of allogeneic antibody variable domains, while preserving ligand-binding properties, by reducing their antigenicity through replacement of the exposed residues in the framework regions which differ from those usually found in host antibodies. The results of a comparison of representative murine antibody sequences with those of human origin suggest that the number of residues that need to be replaced to "\*humanize\*" those antibodies could be small.

31/7/15 (Item 15 from file: 155)  
07757287 91276287

Immunoglobulin complementarity-determining region grafting by recombinant polymerase chain reaction to generate \*humanised\* monoclonal antibodies.

Lewis AP; Crowe JS

Department of Cell Biology, Wellcome Research Laboratories, Beckenham, Kent, U.K.

Gene May 30 1991, 101 (2) p297-302, ISSN 0378-1119 Journal Code:

FOP

Languages: ENGLISH



Document type: JOURNAL ARTICLE

We describe an approach to rapidly generate \*humanised\* monoclonal antibodies by grafting rodent complementarity-determining regions onto human immunoglobulin frameworks using recombinant polymerase chain reaction (PCR) methodology. The approach was applied to grafting a rat complementarity-determining region onto a human framework and amplifying the entire \*humanised\* heavy chain. The terminal oligodeoxyribonucleotide primers incorporated restriction sites to allow forced cloning into plasmid vectors for sequencing and expression. No nucleotide errors were introduced into the 1463-bp sequence even after sequential applications of PCR.

31/7/16 (Item 16 from file: 155)

07668893 91187893

\*Humanized\* antibodies for antiviral therapy.

Co MS; Deschamps M; Whitley RJ; Queen C

Protein Design Labs, Inc., Mountain View, CA 94043.

Proc Natl Acad Sci U S A Apr 1 1991, 88 (7) p2869-73, ISSN 0027-8424

Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Antibody therapy holds great promise for the treatment of cancer, autoimmune disorders, and viral infections. Murine monoclonal antibodies are relatively easy to produce but are severely restricted for therapeutic use by their immunogenicity in humans. Production of human monoclonal antibodies has been problematic. \*Humanized\* antibodies can be generated by introducing the six hypervariable regions from the heavy and light chains of a murine antibody into a human framework sequence and combining it with human constant regions. We \*humanized\*, with the aid of computer modeling, two murine monoclonal antibodies against herpes simplex virus gB and gD glycoproteins. The binding, virus neutralization, and cell protection results all indicate that both \*humanized\* antibodies have retained the binding activities and the biological properties of the murine monoclonal antibodies.

31/7/17 (Item 17 from file: 399)

117024688 CA: 117(3)24688r PATENT

Humanized complementarily-determining region (CDR)-grafted antibodies to intercellular adhesion molecule-1 (ICAM-1), methods of preparation and usage thereof

INVENTOR(AUTHOR): Adair, John Robert; Athwal, Diljeet Singh; Rothlein, Robert A.

LOCATION: UK,

ASSIGNEE: Celltech Ltd.; Boehringer Ingelheim Pharmaceuticals, Inc.

PATENT: PCT International ; WO 9116927 A1 DATE: 911114

APPLICATION: WO 91US2942 (910429) \*GB 909549 (900427)

PAGES: 81 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; C07K-015/28B DESIGNATED COUNTRIES: AT; AU; BB; BG; BR; CA; CH; DE; DK; ES; FI; GB; HU; JP; KP; KR; LK; LU; MC; MG; MW; NL; NO; PL; RO; SD; SE; SU; US DESIGNATED REGIONAL: AT; BE; BF; BJ; CF; CG; CH; CM; DE; DK; ES; FR; GA; GB; GR; IT; LU; ML; MR; NL; SE; SN; TD; TG

SECTION:

CA215003 Immunochemistry

CA201XXX Pharmacology

CA203XXX Biochemical Genetics

IDENTIFIERS: humanized antibody intercellular adhesion mol 1, inflammation inhibitor humanized antibody ICAM1, asthma inhibitor humanized antibody ICAM1, AIDS virus humanized antibody ICAM1, virucide humanized antibody ICAM1, diagnosis humanized antibody ICAM1

DESCRIPTORS:

Dermatitis...

*Get this*

*Q11.N26*

acute, treatment of, with humanized antibody to intercellular adhesion mol.-1

Immunosuppressants...  
and humanized antibody to intercellular adhesion mol.-1, pharmaceutical compn. contg.

Rodent...  
anti-intercellular adhesion mol.-1 antibody variable region complementary detg. region of, in humanized antibody prodn.

Integrins, antigens LFA-1...  
antibody to, and humanized antibody to intercellular adhesion mol.-1, for inflammation treatment

Neoplasm inhibitors, metastasis...  
chimeric antibody to intercellular adhesion mol.-1, for hemopoietic cell tumors

Toxicity...  
cytokine-induced, inflammation of, treatment of, humanized antibody to intercellular adhesion mol.-1 for

Inflammation...  
diagnosis of, with chimeric antibody binding to cell expressing intercellular adhesion mol.-1

Deoxyribonucleic acids...  
for antibody heavy and light chains, in humanized antibody to intercellular adhesion mol.-1 prodn.

Deoxyribonucleic acid sequences...  
for monoclonal antibody R6-5-D6 heavy and light chain components for humanized antiintercellular adhesion mol.-1 antibody

Leukocyte...  
human immunodeficiency virus infection of, inhibition of, with humanized antibody to intercellular adhesion mol.-1

Bronchodilators, antiasthmatics... Inflammation inhibitors... Inflammation inhibitors, antirheumatics... Therapeutics... Virucides and Virustats...  
humanized antibody to intercellular adhesion mol.-1

Toxins...  
humanized antibody to intercellular adhesion mol.-1 derivatized with, for inhibition of intercellular adhesion mol.-1-expressing tumor cell

Diagnosis...  
humanized antibody to intercellular adhesion mol.-1 for

Inflammation inhibitors, antiarthritics...  
humanized antibody to intercellular adhesion mol.-1, for reaction arthritis

Glycoproteins, specific or class, ICAM-1 (intercellular adhesion mol. 1)...  
humanized recombinant antibody to

Antibodies...  
humanized recombinant, to intercellular adhesion mol.-1

Thyroid gland, disease, autoimmune thyroiditis...  
inflammation in, treatment of, with humanized antibody to intercellular adhesion mol.-1

Nervous system, central...  
inflammation of, treatment of, humanized antibody to intercellular adhesion mol.-1 for

Autoimmune disease... Blood vessel, disease, Raynaud's phenomenon...

Brain, disease, stroke... Dialysis, hemo-... Encephalomyelitis...

Intestine, disease, Crohn's... Intestine, disease, pseudomembranous enterocolitis... Intestine, disease, ulcerative colitis... Kidney, disease, acute glomerulonephritis... Leukapheresis... Lupus erythematosus...

Multiple sclerosis... Psoriasis... Respiratory distress syndrome, adult...  
inflammation of, treatment of, with humanized antibody to intercellular adhesion mol.-1

Neoplasm, composition...  
intercellular adhesion mol.-1-expressing, diagnosis of, with humanized

antibody to intercellular adhesion mol.-1  
 Mouse...  
 monoclonal antibody R6-5-D6 of, in humanized antibody to intercellular adhesion mol.-1 prodn.  
 Sepsis and Septicemia...  
 multiple organ injury syndrome secondary to, inflammation of, treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Protein sequences...  
 of monoclonal antibody R6-5-D6 heavy and light chain components for humanized antiintercellular adhesion mol.-1 antibody  
 Plasmid and Episome...  
 pAL5, in grafted humanized antibody to intercellular adhesion mol.-1 prodn.  
 Plasmid and Episome...  
 pAL6, in grafted humanized antibody to intercellular adhesion mol.-1 prodn.  
 Plasmid and Episome...  
 pBJ1, in grafted humanized antibody to intercellular adhesion mol.-1 prodn.  
 Kidney,transplant... Organ,transplant... Transplant and Transplantation...  
 rejection of, inflammation of, treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Antibodies,monoclonal...  
 R6-5-D6, of mouse, in humanized antibody to intercellular adhesion mol.-1 prodn.  
 Organ,disease, multiple organ failure...  
 secondary to septicemia or trauma, treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Temperature effects,biological...  
 thermal injury, inflammation of, treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Perfusion,re-...  
 tissue injury from, treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Lymphokines and Cytokines...  
 toxicity induced by, inflammation of, treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Neoplasm inhibitors...  
 toxin-derivatized humanized antibody to intercellular adhesion mol.-1, for intercellular adhesion mol.-1-expressing tumor cell  
 Leukocyte,granulocyte...  
 transfusion-assocd. syndrome, treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Allergy,delayed hypersensitivity...  
 treatment of, humanized antibody to intercellular adhesion mol.-1 for  
 Picornaviridae... Virus,animal, Coxsackie A... Virus,animal, human immunodeficiency... Virus,animal, human immunodeficiency 1... Virus,animal, Mengo... Virus,animal, rhino-...  
 treatment of infection with, with humanized antibody to intercellular adhesion mol.-1  
 Hematopoietic precursor cell...  
 tumorous, metastasis of, inhibition of, chimeric antibody to intercellular adhesion mol.-1  
 Genetic vectors...  
 with DNA for antibody heavy and light chains, in humanized antibody to intercellular adhesion mol.-1 prodn.  
 CAS REGISTRY NUMBERS:  
 142007-78-1 142007-79-2 142007-80-5 142007-81-6 142007-82-7  
 142007-83-8 142007-85-0 amino acid sequence of  
 142007-84-9 amino acid sequence of, humanized antibody to intercellular

adhesion mol.-1 in relation to  
140876-28-4 140876-29-5 142007-86-1 142007-87-2 amino acid sequence of,  
humanized antibody to intercellular adhesion mol.-1 prodn. in relation  
to  
140857-88-1 142008-94-4 nucleotide sequence of, humanized antibody to  
intercellular adhesion mol.-1 prodn. in relation to  
140857-89-2 142008-93-3 nucleotide sequence of, humanized antibody to  
intercellular adhesion mol.01 prodn. in relation to  
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31/7/18 (Item 18 from file: 155)  
07449972 90356972

Immunoglobulin V regions of a bactericidal anti-Neisseria meningitidis  
outer membrane protein monoclonal antibody.

Larrick JW; Coloma MJ; del Valle J; Fernandez ME; Fry KE;  
Gavilondo-Cowley JV

Genelabs Inc., Redwood City, California.

Scand J Immunol Aug 1990, 32 (2) p121-8, ISSN 0300-9475

Journal Code: UCW

Languages: ENGLISH

Document type: JOURNAL ARTICLE

C6 is a potentially therapeutic murine monoclonal antibody that  
recognizes the class 1 outer membrane protein of Neisseria meningitidis. C6  
specifically immunoblots this antigen and augments in vitro killing of N.  
meningitidis bacteria. We describe a general method of obtaining the heavy  
and light chain variable-region sequence from immunoglobulin-secreting  
cells. The method uses mixed polymerase chain reaction (PCR) primers  
designed from the 5' end of the framework 1 (FR1) sequences of the heavy  
and light chains, and 3'-end primers for constant-region conserved  
sequences. The method has been applied to the cloning and sequencing of the  
variable region of C6 to construct a \*humanized\* monoclonal antibody. Rapid  
amplification and sequencing of variable regions by this general method  
have multiple applications in the study of the immune response to  
infectious diseases.

31/7/19 (Item 19 from file: 155)  
07292738 90199738

Cloning of the genes for T84.66, an antibody that has a high specificity  
and affinity for carcinoembryonic antigen, and expression of chimeric  
human/mouse T84.66 genes in myeloma and Chinese hamster ovary cells.

Neumaier M; Shively L; Chen FS; Gaida FJ; Ilgen C; Paxton RJ; Shively JE;  
Riggs AD

Division of Biology, Beckman Research Institute of the City of Hope,  
Duarte, California 91010.

Cancer Res Apr 1 1990, 50 (7) p2128-34, ISSN 0008-5472

Journal Code: CNF

Contract/Grant No.: CA 43904

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Carcinoembryonic antigen (CEA) is one of the best characterized  
tumor-associated antigens and is extensively used in the in vitro  
immunodiagnosis of human colon adenocarcinomas. Among a number of anti-CEA  
monoclonal antibodies, the murine monoclonal antibody T84.66 shows the  
highest specificity and affinity for CEA and has been used successfully for  
in vivo tumor imaging in mice and humans. We report here the cloning and  
sequencing of the genes coding for monoclonal antibody T84.66 and the amino  
acid sequence of the variable regions for the heavy and light chains. We  
also report the construction of mouse/human chimeric IgG1 antibody genes  
using T84.66 variable region genes and human constant region genes. The  
resulting chimeric gene constructs were transfected into murine myeloma

cells (Sp2/0) by electroporation and into Chinese hamster ovary cells by lipofection. The chimeric antibodies obtained exhibited the same specificity and affinity for CEA as that of the T84.66 immunoglobulin produced by the murine hybridoma cell line. Antibody concentrations in culture medium supernatants were clonally variable but similar (15-480 ng/ml) for both Sp2/0 and Chinese hamster ovary transfectants; the average production by Chinese hamster ovary transfectants was only 3-5-fold less than Sp2/0 transfectants. Ascites production of Sp2/0 transfectants is sufficiently high (900 micrograms/ml) for initial in vivo studies with \*humanized\* T84.66.

31/7/20 (Item 20 from file: 155)

07192290 90099290

A \*humanized\* antibody that binds to the interleukin 2 receptor.

Queen C; Schneider WP; Selick HE; Payne PW; Landolfi NF; Duncan JF; Avdalovic NM; Levitt M; Junghans RP; Waldmann TA

Protein Design Labs, Palo Alto, CA 94304.

Proc Natl Acad Sci U S A Dec 1989, 86 (24) p10029-33, ISSN 0027-8424

Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The anti-Tac monoclonal antibody is known to bind to the p55 chain of the human interleukin 2 receptor and to inhibit proliferation of T cells by blocking interleukin 2 binding. However, use of anti-Tac as an immunosuppressant drug would be impaired by the human immune response against this murine antibody. We have therefore constructed a "\*humanized\*" antibody by combining the complementarity-determining regions (CDRs) of the anti-Tac antibody with human framework and constant regions. The human framework regions were chosen to maximize homology with the anti-Tac antibody sequence. In addition, a computer model of murine anti-Tac was used to identify several amino acids which, while outside the CDRs, are likely to interact with the CDRs or antigen. These mouse amino acids were also retained in the \*humanized\* antibody. The \*humanized\* anti-Tac antibody has an affinity for p55 of  $3 \times 10^9$  M<sup>-1</sup>, about 1/3 that of murine anti-Tac.

*Get this.*

31/7/21 (Item 21 from file: 155)

06533056 88178056

Reshaping human antibodies: grafting an antilysozyme activity.

Verhoeyen M; Milstein C; Winter G

Medical Research Council Laboratory of Molecular Biology, Cambridge, England.

Science Mar 25 1988, 239 (4847) p1534-6, ISSN 0036-8075

Journal Code: UJ7

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The production of therapeutic human monoclonal antibodies by hybridoma technology has proved difficult, and this has prompted the "\*humanizing\*" of mouse monoclonal antibodies by recombinant DNA techniques. It was shown previously that the binding site for a small hapten could be grafted from the heavy-chain variable domain of a mouse antibody to that of a human myeloma protein by transplanting the hypervariable loops. It is now shown that a large binding site for a protein antigen (lysozyme) can also be transplanted from mouse to human heavy chain. The success of such constructions may be facilitated by an induced-fit mechanism.

?save temp

Temp SearchSave "TD101" stored

?b351,350

SYSTEM:OS - DIALOG OneSearch

~~File 351:Derwent World Patents Index Latest~~

1981+;DW=9227,UA=9214,UM=9143

\*\*FILE351: Formats 32,33,35,37 &amp; 39 display the new 'Expanded' Patent Family table for UD=9216 and greater. For more info. type ?NEWS351

~~File 350:Derwent World Patents Index~~

1963-1980, EQUIVALENTS THRU DW=9227

\*\*FILE350: Formats 32,33,35,37 &amp; 39 display the new 'Expanded' Patent Family table for UD=9219 and greater. For more info. type ?NEWS350

Set	Items	Description
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?exs

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HIGHLIGHT set on as '\*'

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2945 ANTIBODIES/TI

S1 0 HUMANIZED()ANTIBODIES/TI

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&gt;&gt;&gt;No valid files specified in FROM

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&gt;&gt;&gt;"S4" does not exist

S2 0 S4

S3 1 HUMANIZ?

S4 26 HUMANIS?

S5 0 S4 AND (HUMANIZ? OR HUMANIS?)

HIGHLIGHT set on as '\*'

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&gt;&gt;&gt;File 73 is not open

&gt;&gt;&gt;File 399 is not open

&gt;&gt;&gt;No valid files specified in FROM

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&gt;&gt;&gt;File 399 is not open

&gt;&gt;&gt;No valid files specified in FROM

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?ss antibod? and (s3 or s4)

S6 13936 ANTIBOD?

1 S3

26 S4

S7 22 ANTIBOD? AND (S3 OR S4)

?ss cdr or (ig or immunoglobulin())variable()region or (complementary())determining

Processing

Processing

S8 31 CDR

S9 786 IG

S10 1576 IMMUNOGLOBULIN  
 S11 108404 VARIABLE  
 S12 108131 REGION  
 S13 4 (IG OR IMMUNOGLOBULIN) (W) VARIABLE (W) REGION  
 S14 23564 COMPLEMENTARY  
 S15 501 DETERMING  
 S16 0 COMPLEMENTARY (W) DETERMING  
 S17 23 HYPERVARIABLE  
 S18 108131 REGION  
 S19 12 (COMPLEMENTARY (W) DETERMING OR HYPERVARIABLE) (W) REGION  
 S20 11218 ANTIBODY  
 S21 43127 RELATED  
 S22 28329 BINDING  
 S23 29492 SITE? ?  
 S24 0 ANTIBODY (W) RELATED (W) BINDING (W) SITE? ?  
 S25 45 CDR OR (IG OR IMMUNOGLOBULIN) () VARIABLE () REGION OR  
 (COMPLEMENTARY () DETERMING OR HYPERVARIABLE) () REGION OR  
 ANTIBODY () RELATED () BINDING () SITE? ?

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26/7/1 (Item 1 from file: 351)  
 009040436 WPI Acc No: 92-167794/21  
 XRAM Acc No: C92-077239

New \*humanised\* \*antibody\* specific for interleukin-2 receptor - with  
 complementarity determin. regions and framework from different  
 immunoglobulin(s), is non immunogenic and used to treat T-cell

Patent Assignee: (PROT-) PROTEIN DESIGN LABS INC

Author (Inventor): QUEEN C L; SELICK H E

Number of Patents: 001

Number of Countries: 001

Patent Family:

CC Number	Kind	Date	Week	
DD 296964	A5	911219	9221	(Basic)

Priority Data (CC No Date): DD 337159 (900117)

Abstract (Basic): DD 296964 A

Compsn. comprises a practically pure human-type immunoglobulin  
 (Ig) that reacts specifically with p55-Tac protein and/or inhibits  
 binding of human interleukin-2 (IL-2) to its specific receptor.

Also new are (1) human-type Ig having 2 pairs of light  
 chain/heavy chain dimers and able to react specifically with an epitope  
 of human IL-2 receptor with affinity at least  $10^8$  M<sup>-1</sup>, in which  
 the complementarity determining regions (\*CDR\*) and human-type frame  
 work regions are from different Ig molecules; (2) \*humanised\* Ig able  
 to bind to IL-2 receptors with one or more \*CDR\* from anti-Tac  
 \*antibody\* in a human framework, where the framework includes  
 at least one amino acid (AA) from anti-Tac; (3) nucleic acid encoding a  
 human Ig framework and murine \*CDR\* which, when expressed, produces an  
 Ig specifically reactive with p55-Tac protein and can block binding of  
 IL-2 to its receptor; (4) cells transformed with this nucleic acid.

USE/ADVANTAGES - These Ig are used to treat humans with  
 T-cell related diseases (e.g. transplant rejection; T-cell leukaemia or  
 autoimmune diseases such as diabetes, multiple sclerosis, etc.). They  
 are specific for the IL-2 receptors; are engineered to be

non-immunising and can be produced by recombinant DNA method. The new Ig are admin. in usual parenteral formulation e.g. in doses of 150 mg for therapy or 0.5-2.5 mg for prophylaxis. Ig can also be used, opt. labelled, for diagnosis; T-cell typing; specific receptor isolation or vaccine prodn. 0/10

Derwent Class: B04; D16;

Int Pat Class: A61K-039/395; C12N-015/13

26/7/2 (Item 2 from file: 351)

009039793 WPI Acc No: 92-167155/20

XRAM Acc No: C92-076891

Prepn. of chimeric \*humanised\* \*antibodies\* - using a new polymerase chain reaction technique; PCR

Patent Assignee: (WELL ) WELLCOME FOUND LTD

Author (Inventor): CROWE J S; LEWIS A P

Number of Patents: 001

Number of Countries: 015

Patent Family:

CC Number	Kind	Date	Week	
WO 9207075	A1	920430	9220	(Basic)

Priority Data (CC No Date): GB 9022011 (901010)

Applications (CC,No,Date): WO 91GB1744 (911008)

Language: English

EP and/or WO Cited Patents: 4.Jnl.Ref; WO 9007861

Designated States

(National): JP; US

(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LU; NL; SE

Abstract (Basic): WO 9207075 A

Prodn. of ds or ss DNA of formula: 5' F1-M-F2 3' encoding an \*antibody\* (Ab) chain or fragment in which at least one of the complementarily determining regions (CDRs) of the variable region is derived from a first mammalian Ab and the framework of the variable region is derived from a second different mammalian Ab, where M is DNA encoding a \*CDR\* of the second Ab and F1 and F2 resp. encode 5' and 3' sequences flanking M, by: (a) prepg. a ss or ds DNA template of formula: 5' f1-H-f2 3' where H is DNA encoding a \*CDR\* of a different specificity from M, and f1 and f2 are homologous to F1 and F2, resp.; (b) obtaining DNA oligonucleotide primers A, B, C and D, where: A comprises the sequence a1 with a 5' end corresp. to the 5' end of F1 and which is identical to the corresp. length of F1 and is oriented in a 5' to 3' direction towards H; B has of the sequence 5' b1-b2 3', where b1 comprises a sequence complementary to a corresp. length of M and has a 3' end complementary to the 5' end of M, and b2 is complementary to a sequence of corresp. length in F1 and has a 5' end which starts at the nucleotide complementary to the 3' end of F1, C has of the sequence 5' c1-c2 3' where c1 comprises a sequence identical to the corresp. length of M and has a 3' end corresp. to the 3' end of M, and c2 is identical to a sequence of corresp. length in F2 and has a 5' end which starts at the nucleotide corresp. to the 5' end of F2, and D comprises a sequence d1 which has a 5' end complementary to the 3' end of F2 and which is complementary to a corresp. length of F2 and is oriented in a 5' to 3' direction towards H, where b1 and c1 overlap by a sufficient length to permit annealing of their 5' ends under conditions which allow PCR to be performed; (c) performing, in any desired order, PCR reactions with primer pairs A, B and C, D on the template prepd. in (a), and (d) mixing the prods. of (c) and performing PCR using primers A and D.

USE/ADVANTAGE - The method allows the prepn. of chimeric, esp. \*humanised\* Abs. The resulting Ab retains the antigen binding



capability of the non-human Ab from which the \*CDR\*(s) are derived.

0/4

Derwent Class: B04; D16;

Int Pat Class: C12N-005/10; C12N-015/12; C12N-015/69; C12P-021/08

26/7/3 (Item 3 from file: 351)

008937440 WPI Acc No: 92-064709/08

XRAM Acc No: C92-029621

New multivalent anti-cytokine immunoglobulins - for treating disorders associated with elevated cytokine levels, e.g. septic and endotoxic shock, AIDS, allergies, etc.; ACQUIRE IMMUNE DEFICIENT SYNDROME

Patent Assignee: (CLLT ) CELLTECH LTD; (CELL-) CELLTECH LTD

Author (Inventor): ALLEN R A; MORGAN S A

Number of Patents: 002

Number of Countries: 035

Patent Family:

CC Number	Kind	Date	Week	
WO 9201472	A	920206	9208	(Basic)
AU 9182381	A	920218	9222	

Priority Data (CC No Date): GB 9015908 (900719)

Applications (CC,No,Date): AU 9182381 (910719); WO 91GB1216 (910719)

Language: English

EP and/or WO Cited Patents: 2.Jnl.Ref; EP 347057; EP 355067; WO 9006371; WO 9007118; WO 9106305

Designated States

(National): AT; AU; BB; BG; BR; CA; CH; CS; DE; DK; ES; FI; GB; HU; JP; KP ; KR; LK; LU; MC; MG; MW; NL; NO; PL; RO; SD; SE; SU; US

(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LU; NL; OA; SE

Filing Details: AU9182381 Based on WO 9201472

Abstract (Basic): WO 9201472

New multivalent immunoglobulin (I) has at least 3 linked antigen-binding domains (ABD's) each being specific for a complementary site on a cytokine.

The combining interactions between ABD and cytokine sites are neutralising. (I) is specific for tumour necrosis factor (TNF) alpha or beta; an interleukin, an interferon or a colony-stimulating factor, and it contains 4-20 ABD.

ABD are all of class IgG (most pref.) or all of class IgM (but must be different from a native IgM molecule) and can be linked by covalent crosslinking (e.g. 2-iminothiolane/ maleimide system) or by non-covalent interaction (e.g. using an \*antibody\* reactive with sites on Ig other than those involved in antigen binding; or the biotin-avidin system). (I) are made by joining together appropriate immunoglobulin molecules or fragments esp \*CDR\*-grafted or \*humanised\* chimaeric Ig. USE/ADVANTAGE- (I) are used to treat or prevent diseases associated with elevated cytokine levels, e.g. immuno regulatory and inflammatory disease, sepsis, endotoxic or cardiovascular shock, AIDS, psoriasis, organ transplant rejection or excessive TNF generation induced cancer therapy etc., Compared with monomeric Ig, (I) have much greater neutralising activity. @(43pp)@

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; A61K-039/395; C07K-015/28; C12P-021/08

26/7/4 (Item 4 from file: 351)

008929605 WPI Acc No: 92-056874/07

Related WPI Accession(s): 91-222915

XRAM Acc No: C92-025713

New \*cdr\*-grafted anti carcinoembryonic antigen \*antibodies\* - useful in therapy and diagnosis of carcinoma

Patent Assignee: (CELL-) CELLTECH LTD

Author (Inventor): ADAIR J R; BODMER M W; MOUNTAIN A; OWENS R J

Number of Patents: 001

Patent Family:

CC Number	Kind	Date	Week
WO 9201059	A	920123	9207 (Basic)

Priority Data (CC No Date): WO 91GB1108 (910705); GB 9014932 (900705); WO 90GB2017 (901221)

Language: English

EP and/or WO Cited Patents: WO 8910140; WO 8901783; EP 323806; 6.Jnl.REF

Designated States

(National): AT; AU; BB; BG; BR; CA; CH; CS; DE; DK; ES; FI; GB; HU; JP; KP  
; KR; LK; LU; MC; MG; MW; NL; NO; PL; RO; SD; SE; SU; US

(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LU; NL; SE; OA

Abstract (Basic): WO 9201059

New \*humanised\* \*antibody\* molecule (HAM) is specific for carcino-embryonic antigen (CEA) and has an antigen binding site in which at least one of the complementarity determining regions (\*CDR\*'s) of the variable domain is derived from the mouse monoclonal \*antibody\* (MAb) A5B7. The remaining Ig-derived parts of HAM are of human origin.

HAM is a chimeric or \*CDR\*-grafted \*humanised\* \*antibody\*, prep'd. by recombinant DNA techniques. It can be a complete \*antibody\* or an Fab, Fab', (Fab')<sub>2</sub> or Fv fragment, or a single-chain fragment. It may have a reporter or effector molecule attached to it.

USE/ADVANTAGE - HAM are useful in therapy or diagnosis (including imaging) of carcinomas which produce CEA, e.g., when coupled to a toxin such as ricin. @ (70pp Dwg.No.0/19)

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; C07K-015/28; C12N-015/13; C12P-021/08

26/7/5 (Item 5 from file: 351)

008849515 WPI Acc No: 91-353533/48

XRAM Acc No: C91-152448

New \*humanised\* \*CDR\*-grafted anti-ICAM \*antibodies\* - used to treat and prevent inflammation (e.g. psoriasis) tumours, viral infections and asthma and in diagnosis; INTER CELLULAR ADHESIVE MOLECULAR

Patent Assignee: (CELL-) CELLTECH LTD; (BOEH ) BOEHRINGER INGELHEIM PHA

Author (Inventor): ADAIR J R; ATHWAL D S; ROTHLEIN R A

Number of Patents: 002

Patent Family:

CC Number	Kind	Date	Week
WO 9116927	A	911114	9148 (Basic)
AU 9179001	A	911127	9210

Priority Data (CC No Date): GB 909549 (900427)

Applications (CC,No,Date): WO 91US2942 (910429)

Language: English

EP and/or WO Cited Patents: US 4816567; WO 8901783; 7.Jnl.REF

Designated States

(National): AT; AU; BB; BG; BR; CA; CH; DE; DK; ES; FI; GB; HU; JP; KP; KR  
; LK; MC; MG; MW; NL; NO; PL; RO; SD; SE; SU; US

(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LU; NL; SE; OA

Abstract (Basic): WO 9116927

A recombinant \*antibody\* molecule comprising antigen binding regions derived from the heavy and/or light chain variable regions of an anti-intracellular adhesion molecule-1 (anti-ICAM-1) \*antibody\* is claimed. The Ab is \*CDR\*-grafted and comprises several non-human residues. Also claimed are DNA encoding an Ab heavy or light chain, a vector comprising the DNA, host cells transformed with the vector and a method for producing the anti-ICAM-1 grafted Ab.

USE/ADVANTAGE - The Abs are used to treat - and prevent

inflammation in e.g. delayed type hypersensitivity, psoriasis, an autoimmune disease e.g. Reynaud's syndrome, autoimmune thyroiditis, EAE, multiple sclerosis, rheumatoid arthritis and lupus erythematosus, tissue or organ transplant or graft rejection. They are also used to treat and prevent tumours, viral infections (e.g. rhinoviruses of the major serotype within the genus Picornaviridae, group A coxsackievirus, a Mengo virus and HIV); asthma and non-specific defence system response, e.g. adult respiratory distress syndrome, CNS inflammatory disorder, multiple organ injury syndrome secondary to septicaemia or trauma, ulcerative colitis and Crohn's disease. Administration can be enteral, parenteral, topical, intranasal or by inhalation. The Abs are also used to diagnose an ICAM-1-expressing tumour cell and inflammation. @ (68pp Dwg.No.0/4

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; C07K-015/28

26/7/6 (Item 6 from file: 351)

008718897 WPI Acc No: 91-222916/30

XRAM Acc No: C91-096865

CD3 specific \*humanised\* recombinant \*antibody\* - is chimeric or \*cdr\* grafted for immunotherapy and diagnosis; COMPLEMENTARY DETERMINE REGION

Patent Assignee: (CELL-) CELLTECH LTD

Author (Inventor): JOLLIFFE L K; ZIVIN R A; ADAIR J R; ATHWAL D S

Number of Patents: 003

Patent Family:

CC Number	Kind	Date	Week	
WO 9109968	A	910711	9130	(Basic)
AU 9170330	A	910724	9143	
GB 2246781	A	920212	9207	

Priority Data (CC No Date): WO 90GB2018 (901221); GB 8928874 (891221); GB 9117611 (910815)

Applications (CC,No,Date): GB 9017611 (901221)

Language: English

EP and/or WO Cited Patents: EP 403156; EP 328404

Designated States

(National): AT; AU; BB; BG; BR; CA; CH; DE; DK; ES; FI; GB; GR; HU; JP; KR ; LK; LU; MC; MG; MW; NL; NO; RO; SD; SE; SU; US

(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LU; NL; SE; OA

Filing Details: GB2246781 Based on WO9109968 (E) (1251CH)

Abstract (Basic): WO 9109968

A recombinant \*antibody\* (RAM) comprising antigen binding regions derived from the heavy and or light chain variable regions of a donor anti- CD3 \*antibody\*. The \*antibody\* preferably has binding affinity similar to that of OKT3. The RAM comprises antigen binding regions from suitable anti-CD3 \*antibodies\* such as rodent e.g. mouse or rat anti-CD3 MAb. The RAM may comprises only the variable region (VH and/or VL) or one or more CDRs of such a MAb.

The RAM is preferably a \*humanised\* \*antibody\* molecule specific for CD3 having an antigen binding site where at least one of the CDRs of the variable domain and usually two more of the CDRs are derived from non human anti-CD3 \*antibody\*. The RAM may be a chimeric or \*CDR\* grafted \*antibody\*. Usually, the donor and acceptor \*antibodies\* are derived from different species. Typically the donor anti CD3 \*antibody\* is non-human (e.g. rodent) and the acceptor \*antibody\* is human. A \*CDR\* grafted \*antibody\* heavy chain comprising variable region with acceptor and donor CD3 binding comprising donor residues at one or more of positions 6, 37, 48 and 94. The \*CDR\* grafted light chain is also claimed.

DNA coding these \*antibodies\* and their production by recombinant DNA technology is claimed.

USE/ADVANTAGE - The \*antibodies\* may be used for treatment or diagnosis of human or veterinary conditions. The \*humanised\* \*antibodies\* do not have the immunologic complications associated with administration of non human \*antibodies\* to human subjects. @ (81pp Dwg.No.0/13)@

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; A61K-049/00; C07K-015/06; C12N-005/10; C12N-015/13; C12P-021/08

26/7/7 (Item 7 from file: 351)

008718896 WPI Acc No: 91-222915/30

Related WPI Accession(s): 92-056874

XRAM Acc No: C92-025713

New \*humanised\* \*antibodies\* comprising \*CDR\* grafted \*antibody\* - with heavy and light chains, for use in vivo therapy and diagnosis;

COMPLEMENTARY DETERMINE REGION

Patent Assignee: (CLLT ) CELLTECH LTD; (CELL-) CELLTECH LTD

Author (Inventor): ADAIR J R; BODMER M W; MOUNTAIN A; OWENS R J; ATHWAL D S ; EMTAGE J S

Number of Patents: 005

Number of Countries: 035

Patent Family:

CC Number	Kind	Date	Week	
WO 9109967.	A	910711	9130	(Basic)
AU 9169740	A	910724	9143	
GB 2246570	A	920205	9206	
WO 9201059	A	920123	9207	
AU 9182005	A	920204	9220	

*June 21*

Priority Data (CC No Date): GB 8928874 (891221); WO 90GB20174 (901221); GB 9014932 (900705)

Applications (CC,No,Date): AU 9182005 (910705); WO 91GB1108 (910705); GB 9017612 (901221)

Language: English

EP and/or WO Cited Patents: EP 239400; EP 323806; EP 328404; EP 403156; 6.Jnl.Ref; WO 8901783; WO 8910140

Designated States

(National): AT; AU; BB; BG; BR; CH; DE; DK; FI; GB; HU; JP; KP; KR; LK; LU ; MC; MG; MW; NL; NO; RO; SD; SE; SU; US; CA; CS; ES; PL

(Regional): AT; BE; CH; DE; FR; GB; GR; IT; LU; NL; OA; SE; DK; ES

Filing Details: AU9182005 Based on WO 9201059

Abstract (Basic): WO 9109967

A \*CDR\* grafted \*antibody\* heavy chain is claimed having a variable region comprising acceptor frame-work and donor antigen binding regions in at least one of positions 6, 23 and/or 24, 48 and/or 49, 71 and/or 73, 75 and/or 76 and/or 78 and 88 and/or 91. Preferably, the heavy chain framework also comprises donor residues at positions 6, 37, 48 and 94. Also claimed is a \*CDR\*-grafted \*antibody\* light chain having a variable region domain comprising acceptor framework and donor antigen binding regions comprising donor residues in at least one of positions 1 and/or 3 and preferably at positions 46 and/or 47. A \*CDR\* grafted \*antibody\* molecule is also claimed comprising at least one \*CDR\* grafted heavy chain and light chain. DNA encoding the \*CDR\* grafted heavy and light chains is also claimed. The heavy or light chains may have an effector or reporter molecule attached e.g. a macrocycle for chelating a metal atom or a toxin such as ricin. The \*CDR\* grafted \*antibodies\* preferably have non-human e.g. rodent donor and human acceptor frameworks.

USE/ADVANTAGE - For use in treatment and diagnosis of human and veterinary conditions. @ (91pp Dwg.No.0/13

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; A61K-039/395; C07K-015/06; C07K-015/28;  
C12N-005/10; C12N-015/13; C12P-021/08; C12R-001/91

26/7/8 (Item 8 from file: 351)

008366799 WPI Acc No: 90-253800/33

XRAM Acc No: C90-109897

Chimaeric immunoglobulin(s) blocking IL-2 binding to receptors -  
comprising human framework and murine complementary determining  
regions, less immunogenic than murine \*antibodies\*

Patent Assignee: (PROT-) PROTEIN DESIGN LABS INC; (PROT-) PROTEIN DESIGN  
LABS

Author (Inventor): QUEEN C L; SELICK H E

Number of Patents: 010

Number of Countries: 034

Patent Family:

CC Number	Kind	Date	Week	
WO 9007861	A	900726	9033	(Basic)
PT 92758	A	900629	9033	
CA 2006865	A	900628	9037	
AU 9051532	A	900813	9044	
ZA 8909956	A	901031	9048	
CN 1043875	A	900718	9115	
FI 9102436	A	910520	9133	
NO 9102385	A	910619	9142	
DK 9101191	A	910619	9143	
JP 4502408	W	920507	9225	

Priority Data (CC No Date): US 290975 (881228); US 310252 (890213)

Applications (CC,No,Date): WO 89US5857 (891228); JP 90503677 (891228); ZA  
899956 (891228)

Language: English; German

EP and/or WO Cited Patents: 7.Jnl.Ref; EP 239400; GB 2188941; US 4816567;  
WO 8901783

Designated States

(National): AT; AU; BB; BG; BR; CH; DE; DK; FI; GB; HU; JP; KP; KR; LK; LU  
; MC; MG; MW; NL; NO; RO; SD; SE; SU

(Regional): AT; BE; CH; DE; ES; FR; GB; IT; LU; NL; OA; SE

Filing Details: JP04502408 Based on WO 9007861

Abstract (Basic): WO 9007861

Compsn. comprises a pure human-like immunoglobulin (Ig) which (a)  
reacts specifically with p55 Tac protein and/or (b) inhibits binding of  
human interleukin-2 (IL-2) to its receptor. Also new are (1) human-like  
Ig having 2 pairs of light/heavy chains and able to react specifically  
with an epitope of a human IL-2 receptor with affinity at least 10  
power 8 per mole, the chains including complementarily determng. regions  
(\*CDR\*'s) and human-like framework regions (FR's), the \*CDR\*'s being  
from different Ig molecules than FR's; (2) \*humanised\* Ig (hIg) which  
can bind to IL-2 receptors and contain at least one \*CDR\* from anti-Tac  
\*antibody\* in a human-like FR contg. at least one amino acid from the  
anti-Tac \*antibody\*; (3) nucleic acid encoding for human-like FR and at  
least one murine \*CDR\*, and (4) cells transfected with nucleic acid.

USE/ADVANTAGE - hIG are not significantly immunogenic in humans;  
are easily and economically produced, and have a longer half-life in  
vivo than mouse \*antibodies\*. They are useful (opt. when attached to a  
cytotoxic agent, for treatment of T-cell mediated disorders, e.g. graft  
or transplant rejection, and autoimmune diseases. LIG can also be used  
in vitro for T-cell typing; isolation of IL-2 receptor bearing cells,  
vaccine prodn., etc. @ (52pp Dwg.No.0/10)@

Abstract (EP): 9142 EP 451216

Compsn. comprises a pure human-like immunoglobulin (Ig) which (a) reacts specifically with p55 Tac protein and/or (b) inhibits binding of human interleukin-2 (IL-2) to its receptor. Also new are (1) human like Ig having 2 pairs of light/heavy chains and able to react specifically with an epitope of a human IL-2 receptor with affinity at least 10<sup>8</sup> per mole, the chains including complementarily determg. regions (\*CDR\*'s) and human-like framework regions (FR's) the \*CDR\*'s being from different Ig molecules than FR's. (2) \*humanised\* IG (hIg) which can bind to IL-2 receptors and contain at least one \*CDR\* from anti-Tac \*antibody\* in a human-like FR contg. at lesdt one amino acid from the anti-Tac \*antibody\*, (3) nucleic acid encoding for human-like FR and at least one murine \*CDR\*, and (4) cells transfected with nucleic acid.

USE/ADVANTAGE - hIG are not significantly immunogenic in humans, are easily and economically produced, and have a longer half-life in vivo than mouse \*antibodies\*. They are useful (opt. when attached to a cytotoxic agent, for treatment of T-cell mediated disorders, e.g. graft or transplant rejection, and autoimmune diseases, LIG can also be used in vitro for T-cell typing, isolation of IL-2 receptor bearing cells, vaccine prodn etc.

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; C07K-007/10; C07K-013/00; C07K-015/14;  
C12N-005/10; C12N-007/01; C12N-015/00; C12P-021/08

?

set cost off

COST = OFF.  
?set hi \*

HILIGHT set on as '\*'  
Hilight option is not available in file(s) 399.  
?show files

File 155: MEDLINE 1966-1992/NOV (9211W1)  
File 5: BIOSIS PREVIEWS 69-92/OCT BA9407: BARRM4307  
(C. BIOSIS 1992)  
File 73: EMBASE (EXCERPTA MEDICA) 74-92/ISS37  
(COPR. ESP BV/EM 1992)  
File 399: CA SEARCH 1967-1992 UD=11710  
(Copr. 1992 by the Amer. Chem. Soc.)

?ds

Set	Items	Description
S1	16	HUMANIZED() ANTIBODIES/TI
S2	332298	ANTIBODIES! FROM 155
S3	2253	IMMUNOGLOBULIN VARIABLE REGION! FROM 155
S4	2253	S2 AND S3
S5	862	HUMANIZ?
S6	2005	HUMANIS?
S7	16	S4 AND (HUMANIZ? OR HUMANIS?)
S8	636823	ANTIBOD? FROM 5,73,399
S9	165469	IMMUNOGLOBULIN
S10	41830	IG
S11	113462	VARIABLE
S12	392448	REGION
S13	862	(IMMUNOGLOBULIN OR IG) (W) VARIABLE (W) REGION
S14	604	CDR
S15	67991	COMPLEMENTARY
S16	112646	DETERMINING
S17	63	COMPLEMENTARY (W) DETERMINING
S18	1904	HYPERVARIABLE
S19	392448	REGION
S20	747	(COMPLEMENTARY (W) DETERMINING OR HYPERVARIABLE) (W) REGION
S21	428778	ANTIBODY
S22	1469126	RELATED
S23	623755	BINDING
S24	544344	SITE? ?
S25	0	ANTIBODY (W) RELATED (W) BINDING (W) SITE? ?
S26	2161	(IMMUNOGLOBULIN OR IG) () VARIABLE () REGION OR CDR OR (COMPLEMENTARY () DETERMINING OR HYPERVARIABLE) () REGION OR ANTIBODY () RELATED () BINDING () SITE? ? FROM 5,73,399
S27	897	S8 AND S26
S28	18	S27 AND (S5 OR S6)
S29	34	S28 OR S7
S30	21	RD (unique items)
S31	21	Sort S30/ALL/PY,D
S32	3165	COMPLEMENTARITY
S33	2005813	DETERMIN?
S34	524927	REGION
S35	358	COMPLEMENTARITY (W) DETERMIN? (W) REGION
S36	12	COMPLEMENTARITY () DETERMIN? () REGION AND (S5 OR S6) AND S8
S37	28	7 OR 36
S38	8	(37 OR 29) NOT 29

*used complementary  
rather than  
complementarity  
in previous  
search.  
Picked a few  
more references here.*

S39 6 RD (unique items)  
S40 6 Sort S39/ALL/PY,D  
?t40/7/1-6

40/7/1 (Item 1 from file: 5)  
9081780 BIOSIS Number: 93066780  
DEVELOPMENT OF \*HUMANIZED\* BISPECIFIC \*ANTIBODIES\* REACTIVE WITH  
CYTOTOXIC LYMPHOCYTES AND TUMOR CELLS OVEREXPRESSING THE HER2 PROTOONCOGENE  
SHALABY M R; SHEPARD H M; PRESTA L; RODRIGUES M L; BEVERLEY P C L;  
FELDMANN M; CARTER P  
DEP. CELL BIOL., GENENTECH, INC., 460 POINT SAN BRUNO BOULEVARD, SOUTH  
SAN FRANCISCO, CALIF. 94080.  
J EXP MED 175 (1). 1992. 217-226. CODEN: JEMEA  
Full Journal Title: Journal of Experimental Medicine  
Language: ENGLISH  
The HER2 protooncogene encodes a 185-kD transmembrane  
phosphoglycoprotein, human epidermal growth factor receptor 2 (p185HER2),  
whose amplified expression on the cell surface can lead to malignant  
transformation. Overexpression of HER2/p185HER2 is strongly correlated with  
progression of human ovarian and breast carcinomas. Recent studies have  
shown that human T cells can be targeted with bispecific \*antibody\* to  
react against human tumor cells in vitro. We have developed a bispecific  
F(ab')<sub>2</sub> \*antibody\* molecule consisting of a \*humanized\* arm with a  
specificity to 185HER2 linked to another arm derived from a murine anti-CD3  
monoclonal \*antibody\* that we have cloned from UCHT1 hybridoma. The  
antigen-binding loops for the anti-CD3 were installed in the context of  
human variable region framework residues, thus forming a fully \*humanized\*  
BsF(ab')<sub>2</sub> fragment. Additional variants were produced by replacement of  
amino acid residues located in light chain \*complementarity\* \*determining\*  
\*region\* 2 and heavy chain framework region 3 of the \*humanized\* anti-CD3  
arm. Flow cytometry analysis showed that the bispecific F(ab')<sub>2</sub> molecules  
can bind specifically to cells overexpressing p185HER2 and to normal human  
peripheral blood mononuclear cells bearing the CD3 surface marker. In  
additional experiments, the presence of bispecific F(ab')<sub>2</sub> caused up to  
fourfold enhancement in the cytotoxic activities of human T cells against  
tumor cells overexpressing p185HER2 as determined by a 51Cr release assay.  
These bispecific molecules have a potential use as therapeutic agents for  
the treatment of cancer.

40/7/2 (Item 2 from file: 399)  
117068366 CA: 117(7)68366p PATENT  
Chimeric and complementarity-determining region-grafted  
anti-carcinoembryonic antigen antibodies and their production  
INVENTOR(AUTHOR): Adair, John Robert; Bodmer, Mark William; Mountain,  
Andrew; Owens, Raymond John  
LOCATION: UK,  
ASSIGNEE: Celltech Ltd.  
PATENT: PCT International ; WO 9201059 A1 DATE: 920123  
APPLICATION: WO 91GB1108 (910705) \*GB 9014932 (900705) \*WO 90GB2017  
(901221)  
PAGES: 70 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12P-021/08A;  
A61K-039/395B; C12N-015/13B; C07K-015/28B DESIGNATED COUNTRIES: AT; AU; BB  
; BG; BR; CA; CH; CS; DE; DK; ES; FI; GB; HU; JP; KP; KR; LK; LU; MC; MG;  
MN; MW; NL; NO; PL; RO; SD; SE; SU; US DESIGNATED REGIONAL: AT; BE; BF; BJ  
; CF; CG; CH; CI; CM; DE; DK; ES; FR; GA; GB; GN; GR; IT; LU; ML; MR; NL;  
SE; SN; TD; TG  
SECTION:  
CA215003 Immunochemistry  
IDENTIFIERS: carcinoembryonic antigen humanized chimeric antibody,



complementarity detg region grafted antibody CEA, cloning DNA humanized antibody CEA

DESCRIPTORS:

Antibodies, monoclonal...

A5B7 murine, to carcinoembryonic antigen, in humanized antibody prodn.

Animal cell line...

CHO L761 h, humanized anti-carcinoembryonic antigen antibody recombinant prodn. in

Deoxyribonucleic acid sequences...

for antibody variable regions in humanized anti-carcinoembryonic antigen antibody prodn.

Genetic vectors... Molecular cloning...

for humanized anti-carcinoembryonic antigen antibody prodn.

Diagnosis... Therapeutics...

humanized anti-carcinoembryonic antigen antibodies for

Escherichia coli...

humanized anti-carcinoembryonic antigen antibody fragment recombinant prodn. in

Animal cell line, CHO-K1... Animal cell line, COS-1... Bacteria...

humanized anti-carcinoembryonic antigen antibody recombinant prodn. in

Mammal...

humanized anti-carcinoembryonic antigen antibody recombinant prodn. in cells of

Immunoglobulins, fusion products...

humanized, prodn. of

Antibodies...

humanized, to carcinoembryonic antigen

Immunoglobulins...

in humanized anti-carcinoembryonic antigen antibody prodn.

Protein sequences...

of antibody variable regions in humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pAL43, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pAL44, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pAL45, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pAL46, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pAL53, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pAL54, for humanized anti-carcinoembryonic antigen antibody prodn.

Genetic vectors...

pEE6hCMV gpt, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pHMC19, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pHMC30, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pHMC31, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pHMC43, for humanized anti-carcinoembryonic antigen antibody prodn.

Plasmid and Episome...

pHMC44, for humanized anti-carcinoembryonic antigen antibody prodn.

Genetic vectors...

pMRR028, for humanized anti-carcinoembryonic antigen antibody fragment prodn.

Genetic vectors...

pMRR045, for humanized anti-carcinoembryonic antigen antibody fragment  
prodn.

CAS REGISTRY NUMBERS:

142661-53-8 142661-54-9 142661-55-0 142661-56-1 142661-57-2  
142661-58-3 amino acid sequence of, humanized anti-carcinoembryonic  
antigen antibody prodn. in relation to  
142662-69-9 142662-70-2 142662-71-3 142662-72-4 142662-81-5  
142662-82-6 nucleotide sequence of, humanized anti-carcinoembryonic  
antigen antibody prodn. in relation to

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40/7/3 (Item 3 from file: 5)

8599131 BIOSIS Number: 92064131

IMMUNOGLOBULIN \*COMPLEMENTARITY\*--\*DETERMINING\* \*REGION\* GRAFTING BY  
RECOMBINANT POLYMERASE CHAIN REACTION TO GENERATE \*HUMANIZED\* MONOCLONAL  
\*ANTIBODIES\*

LEWIS A P; CROWE J S

DEP. CELL BIOLOGY, WELLCOME RES. LAB., LANGLEY COURT, BECKENHAM, KENT,  
BR3 3BS UK.

GENE (AMST) 101 (2). 1991. 297-302. CODEN: GENED

Full Journal Title: GENE (Amsterdam)

Language: ENGLISH

We describe an approach to rapidly generate \*humanised\* monoclonal  
\*antibodies\* by grafting rodent complementarity-determining regions into  
human immunoglobulin frameworks using recombinant polymerase chain reaction  
(PCR) methodology. The approach was applied to grafting a rat  
\*complementarity\*--\*determining\* \*region\* onto a human framework and  
amplifying the entire \*humanised\* heavy chain. The terminal  
oligodeoxyribonucleotide primers incorporated restriction sites to allow  
forced clonign into plasmid vectors for sequencing and expression. No  
nucleotide errors were introduced into the 1463-bp sequence even after  
sequential applications of PCR.

40/7/4 (Item 4 from file: 5)

7912269 BIOSIS Number: 40113269

CONSTRUCTION OF \*HUMANIZED\* \*ANTIBODIES\* AND TESTING IN PRIMATES

QUEEN C; CO M S; DESCHAMPS M; WHITLEY R; BENJAMIN W; HAKIMI J

PROTEIN DESIGN LAB. INC., 2375 GARCIA AVE., MOUNTAIN VIEW, CALIF. 94043.

MEETING ON MONOCLONAL ANTIBODIES HELD AT THE 20TH ANNUAL MEETING OF THE  
KEYSTONE SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, DENVER, COLORADO, USA,  
MARCH 10-16, 1991. J CELL BIOCHEM SUPPL 15 (PART E) 1991. 137. CODEN:  
JCBSD

Language: ENGLISH

40/7/5 (Item 5 from file: 5)

7400987 BIOSIS Number: 89052006

A \*HUMANIZED\* \*ANTIBODY\* THAT BINDS TO THE INTERLEUKIN 2 RECEPTOR

QUEEN C; SCHNEIDER W P; SELICK H E; PAYNE P W; LANDOLFI N F; DUNCAN J F;

AVDALOVIC N M; LEVITT M; JUNGHANS R P; WALDMANN T A

PROTEIN DESIGN LABS., 3181 PORTER DRIVE, PALO ALTO, CALIF. 94304.

PROC NATL ACAD SCI U S A 86 (24). 1989. 10029-10033. CODEN: PNASA

Full Journal Title: Proceedings of the National Academy of Sciences of  
the United States of America

Language: ENGLISH

The anti-Tac monoclonal \*antibody\* is known to bind to the p55 chain of  
the human interleukin 2 receptor and to inhibit proliferation of T cells by  
blocking interleukin 2 binding. However, use of anti-Tac as an  
immunosuppressant drug would be impaired by the human immune response

against this murine \*antibody\*. We have therefore constructed a "  
\*humanized\*" \*antibody\* by combining the complementarity-determining  
regions (CDRs) of the anti-Tac \*antibody\* with human framework and constant  
regions. The human framework regions were chosen to maximize homology with  
the anti-Tac \*antibody\* sequence. In addition, a computer model of murine  
anti-Tac was used to identify several amino acids which, while outside the  
CDRs, are likely to interact with the CDRs or antigen. These mouse amino  
acids were also retained in the \*humanized\* \*antibody\*. The \*humanized\*  
anti-Tac \*antibody\* has an affinity for p55 of 3 .times. 10<sup>9</sup> M<sup>-1</sup>, about  
1/3 that of murine anti-Tac.

40/7/6 (Item 6 from file: 399)

113170316 CA: 113(19)170316b PATENT

Recombinant antibodies to Campath-1 antigen, containing foreign  
complementarity determining region(s), and their use in immunosuppression  
and cancer therapy

INVENTOR(AUTHOR): Waldmann, Herman; Clark, Michael Ronald; Winter,  
Gregory Paul; Riechmann, Lutz

LOCATION: UK,

ASSIGNEE: Medical Research Council

PATENT: PCT International ; WO 8907452 A1 DATE: 890824

APPLICATION: WO 89GB113 (890210) \*GB 883228 (880212) \*GB 884464 (880225)

PAGES: 61 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A;

C12N-015/00B DESIGNATED COUNTRIES: AU; DK; JP; US

SECTION:

CA215003 Immunochemistry

CA201XXX Pharmacology

CA203XXX Biochemical Genetics

IDENTIFIERS: chimeric antibody Campath 1 antigen, lymphoma neoplasm  
inhibitor Campath 1H antibody

DESCRIPTORS:

Rat...

complementarity detg. regions of, in recombinant antibody to Campath-1  
antigen

Immunoglobulins,G2... Immunoglobulins,G3... Immunoglobulins,G4...

const. domains of human, in recombinant antibody contg. complementarity  
detg. regions to Campath-1 antigen

Lymphocyte...

depletion of, in human, by recombinant human antibody contg. foreign  
complementarity detg. regions to Campath-1 antigen

Gene and Genetic element,animal, synthetic...

for humanized light chain variable region, construction of, in prodn.  
of recombinant human antibody contg. rat complementarity detg. regions  
to Campath-1 antigen

Protein sequences...

of IgG2a YTH 34.5 HL heavy and light chain variable domains, of rat

Deoxyribonucleic acid sequences,IgG2a-specifying...

of rat

Antigens,CAMPATH-1...

recombinant antibodies to, foreign complementarity detg. regions in  
Immunosuppressants... Neoplasm inhibitors... Neoplasm inhibitors,lymphoma

...

recombinant antibody contg. foreign complementarity detg. regions to  
Campath-1 antigen as

Gene and Genetic element,animal...

recombinant, for anti-Campath-1 antigen antibody of human, sequences  
encoding rat complementary detg. regions in

Immunoglobulins,G2a...

recombinant human antibody to Campath-1 antigen contg. complementary  
detg. regions of rat

Leukemia,B-cell...

recombinant human antibody to Campath-1 antigen killing leukemia cells  
of

Antibodies...

recombinant, to Campath-1 antigen, foreign complementarity detg.  
regions in

Immunoglobulins,G1... Immunoglobulins,G... Immunoglobulins,M...

recombinant, to Campath-1 antigen, foreign complementary detg. regions  
in

CAS REGISTRY NUMBERS:

129711-40-6 amino acid sequence encoded by HuVLLYS gene  
129711-41-7 amino acid sequence encoded by synthetic HuVLLYS.degree. gene  
129711-01-9 129711-02-0 cloning and nucleotide sequence of, of human and  
rat  
129711-19-9 129711-20-2 cloning and nucleotide sequence of, of rat  
128096-06-0 128096-07-1 128096-08-2 128096-09-3 128096-10-6  
128096-11-7 complementarity detg. region of rat YTH 34.5 HL, human  
recombinant antibody contg., Campath-1 antigen binding by  
129711-56-4 heavy chain variable region of human contg. rat  
complementarity detg. regions, recombinant antibody contg., Campath-1  
antigen binding by  
129711-60-0 heavy chain variable region of rat YTH 34.5 HL, recombinant  
antibody contg., Campath-1 antigen binding by  
129710-86-7P HuVLLYS gene, prepn. of, in prepn. of recombinant human  
antibody contg. rat complementarity detg. regions to Campath-1 antigen  
129711-59-7 light chain variable region of human contg. rat  
complementarity detg. regions, recombinant antibody contg., Campath-1  
antigen binding by  
129711-61-1 light chain variable region of rat YTH 34.5 HL, recombinant  
antibody contg., Campath-1 antigen binding by  
127859-21-6P 127859-23-8P 127859-24-9P 127859-26-1P 127859-62-5P  
127859-70-5P 127859-72-7P 127859-79-4P 127859-82-9P 127859-92-1P  
127859-93-2P 127859-94-3P 127859-99-8P 127860-01-9P 127860-02-0P  
127860-03-1P 127860-04-2P 129924-57-8P 129924-59-0P prepn. of, in  
gene synthesis for recombinant human antibody contg. rat  
complementarity detg. regions to Campath-1 antigen  
129711-57-5 129711-58-6 recombinant human antibody contg., Campath-1  
antigen binding by  
129710-91-4P synthetic gene HuVLLYS.degree., prepn. of, in prepn. of  
recombinant human antibody contg. rat complementary detg. regions to  
Campath-1 antigen

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?b351,350

15sep92 10:26:26 User209197 Session D127.2

SYSTEM:OS - DIALOG OneSearch

File 351:Derwent World Patents;Index Latest

1981+;DW=9227,UA=9214,UM=9143

\*\*FILE351: Formats 32,33,35,37 & 39 display the new 'Expanded' Patent  
Family table for UD=9216 and greater. For more info. type ?NEWS351

File 350:Derwent World Patents Index

1963-1980, EQUIVALENTS THRU DW=9227

\*\*FILE350: Formats 32,33,35,37 & 39 display the new 'Expanded' Patent  
Family table for UD=9219 and greater. For more info. type ?NEWS350

Set Items Description

--- -----

?ds

Set	Items	Description
S1	22	ANTIBOD? AND (HUMANIS? OR HUMANIZ?)
S2	8	S1 AND (CDR OR (IG OR IMMUNOGLOBULIN) () VARIABLE() REGION OR HYPERVARIABLE() REGION)
S3	0	S1 AND COMPLEMENTARITY() DETERMIN?() REGION
S4	3	S1 AND COMPLEMENT?() DETERMIN?() REGION
S5	1	(2 OR 4) NOT 2

?t5/7/1

5/7/1 (Item 1 from file: 351)  
 007820291 WPI Acc No: 89-085403/11  
 XRAM Acc No: C89-037905

Recombinant \*humanised\* \*antibody\* specific for TAG-72 - having  
 complementarity determining regions of variable domains from mouse  
 \*antibody\* and the remainder from human immunoglobulin

Patent Assignee: (CELL-) CELLTECH LTD

Author (Inventor): BODMER M W; ADAIR J R; WHITTLE N R

Number of Patents: 001

Patent Family:

CC Number	Kind	Date	Week
WO 8901783	A	890309	8911 (Basic)

Priority Data (CC No Date): WO 88GB731 (880905); GB 8720833 (870904)

Language: English

EP and/or WO Cited Patents: No.SR.Pub; 4.Jnl.REF

Designated States

(National): AU; DK; FI; HU; JP; KR; NO; RO; SU; US

(Regional): AT; BE; CH; DE; FR; GB; IT; LU; NL; SE

Abstract (Basic): WO 8901783

A \*humanised\* \*antibody\* molecule (HAM) is claimed having  
 specificity for the TAG-72 antigen and having an antigen binding site  
 in which at least the \*complementary\* \*determining\* \*region\* (CDRs) of  
 the variable domains are derived from the mouse monoclonal \*antibodies\*  
 (MAb) B72.3 and the remaining immunoglobulin-derived parts of the HAM  
 are derived from a human immunoglobulin.

USE/ADVANTAGE - \*Humanising\* the B72.3 MAb does not adversely  
 affect its binding activity and this produces a HAM which is useful in  
 both therapy and diagnosis of certain carcinomas, e.g. solid tumours  
 expressing TAG-72. @ (49pp Dwg.No.0/13)@

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; C12N-015/00; C12P-021/00

?s complement?()determin?(w)region? ?

Processing

Processing

Processing

27431 COMPLEMENT?

234285 DETERMIN?

124968 REGION? ?

S6 23 COMPLEMENT?() DETERMIN?(W) REGION? ?

?c 1 and 6

22 1

23 6

S7 10 1 AND 6

?

?c 7 not (2 or 4)

10 7  
8 2  
3 4  
S8 3 7 NOT (2 OR 4)  
?t8/7/1-3

8/7/1 (Item 1 from file: 351)  
009004842 WPI Acc No: 92-132139/16  
XRAM Acc No: C92-061892

\*Humanisation\* of \*antibodies\* binding to human CD4 antigen - by  
mutation of framework-encoding regions of DNA encoding variable domain  
of rat or mouse \*antibody\* chain

Patent Assignee: (GORM/) GORMAN S D

Author (Inventor): CLARK M R; COBBOLD S P; GORMAN S D; WALDMANN H

Number of Patents: 001

Number of Countries: 018

Patent Family:

CC Number	Kind	Date	Week	
WO 9205274	A	920402	9216	(Basic)

Priority Data (CC No Date): GB 9020282 (900917)

Applications (CC,No,Date): WO 91GB1578 (910916)

Language: English

EP and/or WO Cited Patents: 7.Jnl.Ref; EP 328404; EP 365209; EP 403156; WO  
9007861; WO 9107492; WO 9109966; WO 9109967

Designated States

(National): AU; CA; JP; KR; US

(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LU; NL; SE

Abstract (Basic): WO 9205274 A

\*Complementarity\* \*determining\* \*regions\* (CDRs) of the variable  
domain of the \*antibody\* chain are derived from a first mammalian  
species and the framework of the variable domain and any constant  
domains of the Ab chain are derived from a second different mammalian  
species; comprising (a) mutating the framework-encoding regions of DNA  
encoding a variable domain of the first mammalian Ab chain such that it  
encodes the framework derived from the second species; and (b)  
expressing the Ab chain using this mutated DNA.

The process specifically comprises: (i) determining  
nucleotide and predicted aminoacid sequence of a variable domain of a  
selected Ab chain of the first species; (ii) determining the Ab  
framework to which the framework of this domain is to be altered; (iii)  
mutating framework-encoding regions of DNA encoding this variable  
domain such that the mutated region encodes the framework determined in  
(ii); (iv) linking mutated DNA to DNA encoding a constant domain of the  
second species and cloning the DNA into an expression vector; and (v)  
introducing expression vector into a compatible host cell and culturing  
it to express Ab chain.

USE/ADVANTAGE - Altered Abs is prepd., used to \*humanise\* an  
Ab, typically a monoclonal Ab and, e.g. a rat or mouse Ab. The  
resulting Ab retains the antigen binding capabilities of the Ab from  
which it is derived. Reshaped CD4 Ab is used to induce tolerance  
against an antigen. Used to alleviate autoimmune diseases e.g.  
rheumatoid arthritis, and to prevent graft rejection. 0/13

Derwent Class: B04; D16;

Int Pat Class: A61K-039/39; C12N-015/13; C12P-021/08

8/7/2 (Item 2 from file: 351)  
008712964 WPI Acc No: 91-216983/30

XRAM Acc No: C91-094177

Prodn. of \*humanised\* recombinant immunoglobulin - including polymerase chain reaction amplification of murine \*antibody\* light and heavy chain variable portions

Patent Assignee: (MERI ) MERCK & CO INC

Author (Inventor): LAW M F; MARK G E; WILLIAMSON A R

Number of Patents: 002

Patent Family:

CC Number	Kind	Date	Week
EP 438310	A	910724	9130 (Basic)
CA 2034553	A	910720	9139

Priority Data (CC No Date): US 627423 (901220); US 467700 (900119)

Applications (CC,No,Date): EP 91300362 (910117)

Language: English

EP and/or WO Cited Patents: EP 239400; WO 8901783; 1.Jnl.REF

Designated States

(Regional): CH; DE; FR; GB; IT; LI; NL

Abstract (Basic): EP 438310

Method for producing a \*humanised\* recombinant immunoglobulin comprises: (a) prepg. polymerase chain reaction (PCR) primers to amplify the variable portion of the light and heavy chain of a murine \*antibody\* which binds to a predefined antigen; (b) using the primers to amplify the variable portions of both heavy and light chains and sequencing the resulting nucleotide chains; (c) determining the murine \*complementary\* \*determining\* \*regions\* of the heavy and light chains; (d) selecting human variable heavy and light chain frameworks which show a high degree of amino acid similarity with the variable heavy and light chain framework of the murine immunoglobulin; (e) selecting human constant heavy and light chain frameworks; (f) grafting the murine \*complementary\* \*determining\* \*regions\* of (c) to the human framework regions of (e); (g) incorporating the complete DNA sequence for the \*humanised\* recombinant immunoglobulin into an appropriate expression vector; (h) transfecting host cells with the vector; (i) growing the transfected cells in an environment in which the \*humanised\* recombinant immunoglobulin is expressed; and (j) collecting the immunoglobulin.

A PCR method for the simultaneous synthesis and assembly of at least 4 deoxyoligonucleotides is also claimed.

USE/ADVANTAGE - The \*humanised\* recombinant immunoglobulins are weakly immunogenic or non-immunogenic when admin. to humans, and may be used as therapeutic agents. Recombinant human anti-CD18 \*antibodies\* or active fragments which bind to the CD18 antigen of leukocytes can be used to inhibit influx of the leukocytes into a site of inflammation or tissue liable to become inflamed following influx. @(78pp Dwg.No.0/38)@

Derwent Class: B04; D16;

Int Pat Class: C12N-015/13; C12P-021/08; C12Q-001/68

8/7/3 (Item 3 from file: 351)

007275804 WPI Acc No: 87-272811/39

XRAM Acc No: C87-115825

Recombinant altered \*antibodies\* - having \*complementarity\* \*determining\* \*regions\* replaced with those from \*antibody\* of different specificity

Patent Assignee: (WINT/) WINTER G P

Author (Inventor): WINTER G P

Number of Patents: 004

Patent Family:

CC Number	Kind	Date	Week
EP 239400	A	870930	8739 (Basic)
GB 2188638	A	871007	8740

JP 62296890 A 871224 8806  
 GB 2188638 B 900523 9021  
 Priority Data (CC No Date): GB 867679 (860327); GB 877252 (870326)  
 Applications (CC,No,Date): EP 87302620 (870326); JP 8773980 (870327)  
 Language: English  
 EP and/or WO Cited Patents: A3...8914; 3.Jnl.REF  
 Designated States  
 (Regional): AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE  
 Abstract (Basic): EP 239400

An altered \*antibody\* in which at least parts of the  
 \*complementary\* \*determining\* \*regions\* (CDRs) in the light or heavy  
 chain variable domains have been replaced by analogous parts of CDRs  
 from an \*antibody\* of different specificity is new.

The altered \*antibody\* can be produced by (a) prepg. a first  
 replicable expression vector including a suitable promoter operably  
 linked to a DNA sequence which encodes at least a variable domain of an  
 Ig heavy or light chain, the variable domain comprising framework  
 regions from a first \*antibody\* and CDRs comprising at least parts of  
 the CDRs from a second \*antibody\* of different specificity, (b) if  
 necessary, prepg. a second replicable expression vector including a  
 suitable promoter operably linked to a DNA sequence which encodes at  
 least the variable domain of a complementary Ig light or heavy chain,  
 (c) transforming a cell line with the first or both prepd. vectors and  
 (d) culturing the transformed cell line to produce the altered  
 \*antibody\*.

USE/ADVANTAGE - The method is used for '\*humanising\*' non-human  
 monoclonal \*antibodies\* (MAbs) e.g. CDRs from mouse MAb can be  
 partially or totally grafted into the framework regions of a human MAb,  
 which is then produced in quantity by a suitable cell line. Only the  
 CDRs of the \*antibody\* will be foreign to the body and this should  
 minimise side effects if used for human therapy. @(41pp Dwg.No.0/8)@

Derwent Class: B04; D16;

Int Pat Class: C12N-015/00; C12P-021/02; C07K-015/00; A61K-039/39;  
 C12N-005/00; C12R-001/91

?ds

Set	Items	Description
S1	22	ANTIBOD? AND (HUMANIS? OR HUMANIZ?)
S2	8	S1 AND (CDR OR (IG OR IMMUNOGLOBULIN)()VARIABLE()REGION OR HYPERVARIABLE()REGION)
S3	0	S1 AND COMPLEMENTARITY()DETERMIN?()REGION
S4	3	S1 AND COMPLEMENT?()DETERMIN?()REGION
S5	1	(2 OR 4) NOT 2
S6	23	COMPLEMENT?()DETERMIN?(W)REGION? ?
S7	10	1 AND 6
S8	3	7 NOT (2 OR 4)
S9	5	S1 AND CDRS
S10	0	(9 OR 7 OR 2 OR 4) NOT (7 OR 2 OR 4)

?